PATENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
PWO-18506		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/JP 99/03602	02/07/1999	06/07/1998
Applicant		
FUJISAWA PHARMACEUTICAL CO., LTD. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   USE OF FK506 AND RELATED MACROLIDES IN THE MANUFACTURE OF A MEDICAMENT FOR TREATMENT OR PREVENTION OF PAIN

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 99/03602

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/445 A61K31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 859 782 A (HIGA TATSUO ET AL) 22 August 1989 (1989-08-22) column 15, line 11 ---	1-9
X	WO 96 13249 A (SANDOZ LTD ;SANDOZ AG (AT); SANDOZ AG (AT); JACKMAN MARTIN (CH); P) 9 May 1996 (1996-05-09) page 2, line 12 -page 5, line 6; claims 1-8; examples 13-30 ---	4,6
X	EP 0 753 297 A (FUJISAWA PHARMACEUTICAL CO) 15 January 1997 (1997-01-15) claims 1-15 page 9, line 1 - line 2 --- -/--	1-9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 November 1999	12/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Uiber, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 99/03602

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 664 130 A (SENJU PHARMA CO) 26 July 1995 (1995-07-26) column 2, line 42 - line 44 claims 1-3 column 4, line 28 - line 32	1,3-5

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 99/03602

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4859782 A	22-08-1989	EP 0270660 A	15-06-1988
		JP 1500517 T	23-02-1989
		WO 8800195 A	14-01-1988
WO 9613249 A	09-05-1996	AU 3845195 A	23-05-1996
		BR 9509530 A	14-10-1997
		CA 2200966 A	09-05-1996
		CZ 9701232 A	13-08-1997
		DE 19581804 T	22-01-1998
		EP 0786986 A	06-08-1997
		FI 971018 A	18-04-1997
		GB 2308546 A,B	02-07-1997
		HU 77140 A	02-03-1998
		JP 10508588 T	25-08-1998
		NO 971951 A	25-04-1997
		NZ 295170 A	25-02-1999
		PL 319599 A	18-08-1997
		SK 52097 A	10-09-1997
		GB 2327610 A,B	03-02-1999
EP 0753297 A	15-01-1997	JP 6345646 A	20-12-1994
		AU 684286 B	11-12-1997
		AU 6816294 A	03-01-1995
		CN 1124925 A	19-06-1996
		WO 9428894 A	22-12-1994
		US 5939427 A	17-08-1999
EP 0664130 A	26-07-1995	CA 2120917 A	29-04-1993
		WO 9307884 A	29-04-1993

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 01 February 2000 (01.02.00)	
International application No. PCT/JP99/03602	**Applicant's or agent's file reference** PWO-18506
International filing date (day/month/year) 02 July 1999 (02.07.99)	**Priority date** (day/month/year) 06 July 1998 (06.07.98)
Applicant KELLY, John, S. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

30 December 1999 (30.12.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Sean Taylor
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

TABUSHI, Eiji
Fujisawa Pharmaceutical Co., Ltd.
Osaka Factory
1-6, Kashima 2-chome
Yodogawa-ku, Osaki-shi
Osaka 532-8514
JAPON

Date of mailing (day/month/year) 01 September 1999 (01.09.99)	
Applicant's or agent's file reference PWO-18506	**IMPORTANT NOTIFICATION**
International application No. PCT/JP99/03602	International filing date (day/month/year) 02 July 1999 (02.07.99)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 06 July 1998 (06.07.98)
Applicant FUJISAWA PHARMACEUTICAL CO., LTD. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
06 July 1998 (06.07.98)	9814640.0	GB	06 Augu 1999 (06.08.99)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Carlos Naranjo

Telephone No. (41-22) 338.83.38

Form PCT/IB/304 (July 1998)

002821314

6

PATENT COOPERATION TREATY

RECD 17 OCT 2000
WIPO PCT

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PWO-18506		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP99/03602	02/07/1999	06/07/1998
International Patent Classification (IPC) or national classification and IPC A61K31/445		
Applicant FUJISAWA PHARMACEUTICAL CO., LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30/12/1999	13.10.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Uiber, P Telephone No. +49 89 2399 8474

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/JP99/03602

I. Basis f the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-16 as originally filed

Claims, No.:

1-9 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 3,5.

because:

☒ the said international application, or the said claims Nos. 3,5 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separat sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2,8,9
	No:	Claims	1,3-7
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-9
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

s e separate sheet

SECTION III

1). Claims 3 and 5 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

SECTION V

2). The following documents (D1-D4) are referred to in this International Preliminary Examination Report (IPEA); the numbering results from the order of citations found in the Search Report and it will be adhered to in the rest of the procedure. **It will be made reference to the cited passage(s) for each citation unless otherwise specified.**

3). For the assessment of the present claims 3 and 5 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4). a) The subject matter of claims 1 and 3-7 lacks novelty over D1-D4 (Art. 33(2) PCT). Pharmaceutical compositions containing a macrolide as an active ingredient, such as FK506 and related derivatives and the use of macrolides as analgesic are already known from D1-D4.

b) It seems that the subject matter of claims 2 and 8-9 is novel over D1-D4 (Art. 33(2) PCT). The use of FK506 in the treatment of pain or in the treatment of arthritis-pain has never been reported in D1-D4. D3 is reporting the treatment of chronic rheumatoid arthritis (CRA) by topical administration of FK506 but is silent as to the treatment of the pain related to CRA.

5). a) According to D1, misakinolide macrolides are effective analgesic agents. Likewise, upon administration of nystatin to a patient suffering of haemorrhoid, alleviation of pain was reported by D4.

Based on that, it appears that macrolide may have a positive effect on pain. Moreover, FK506 and related derivatives have been successfully used in the treatment of chronic rheumatoid arthritis (D3). Accordingly, D1 (or D4) when combined with D3 makes the subject matter of claims 2, 6 and 8-9 obvious. The subject matter of claims 2 and 8-9 does not meet the requirement of Art. 33(3) PCT.

SECTION VII

6). Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D4 are not mentioned in the description, nor are these documents identified therein.

A.D.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/445, 31/435 — A1

(11) International Publication Number: **WO 00/01385**

(43) International Publication Date: 13 January 2000 (13.01.00)

(21) International Application Number: PCT/JP99/03602

(22) International Filing Date: 2 July 1999 (02.07.99)

(30) Priority Data:
9814640.0 6 July 1998 (06.07.98) GB

(71) Applicant *(for all designated States except US)*: FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4–7, Doshomachi 3–chome, Chuo–ku, Osaka–shi, Osaka 541–8514 (JP).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: KELLY, John, S. [GB/GB]; University of Edinburgh, 1 George Square, Edinburgh EH8 9JZ (GB). MCQUEEN, Daniel, S. [GB/GB]; University of Edinburgh, 1 George Square, Edinburgh EH8 9JZ (GB).

(74) Agent: TABUSHI, Eiji; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1–6, Kashima 2–chome, Yodogawa–ku, Osaka–shi, Osaka 532–8514 (JP).

(81) Designated States: BR, CA, CN, JP, KR, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: USE OF FK506 AND RELATED MACROLIDES IN THE MANUFACTURE OF A MEDICAMENT FOR TREATMENT OR PREVENTION OF PAIN

(57) Abstract

Macrolide compounds, such as the FK506 Substance and its related compounds are provided for use as an analgesic, particularly, a topical analgesic. Composition containing such compounds is also disclosed.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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DESCRIPTION

USE OF FK506 AND RELATED MACROLIDES IN THE MANUFACTURE OF A MEDICAMENT FOR TREATMENT OR PREVENTION OF PAIN

TECHNICAL FIELD

This invention relates to a new use of macrolide compounds as an analgesic.

BACKGROUND ART

The macrolide compound and its pharmaceutically acceptable salt for use in accordance with this invention is known to have excellent immunosuppressive activity, and, as such, be of value for the treatment or prevention of rejection reactions by transplantation of organs or tissues, graft-vs.-host diseases, autoimmune diseases, and so on [EP-A-0184162, EP-A-0323042, etc].

DISCLOSURE OF INVENTION

The inventors of this invention have surprisingly found that the macrolide compounds mentioned herein below have an analgesic effect, especially topical analgesic effect, and thereby are useful as an analgesic.

Accordingly, this invention provides a new use of the macrolide compounds as an analgesic.

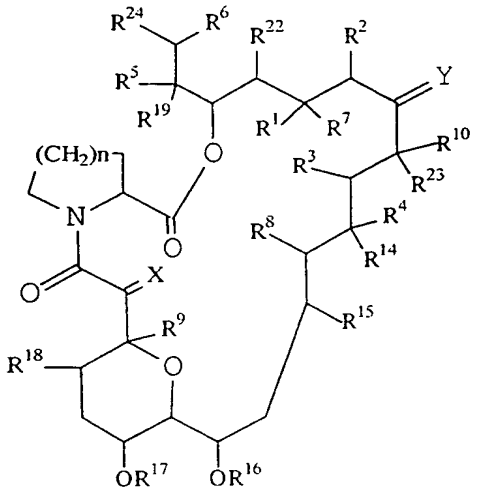
Further, this invention provides an analgesic, which comprises the macrolide compounds.

Still further, this invention provides a method for preventing or treating pain, which comprises administering said macrolide compounds to mammals.

The term "macrolide compound" for use in accordance with the invention is the generic name of compounds with 12 members or more, which belong to macrocyclic lactones.

As a particular example of the macrolide compound, the

tricyclic compound of the following formula (I) can be exemplified.



(I)

(wherein each of adjacent pairs of R^1 and R^2, R^3 and R^4, and R^5 and R^6 independently

(a) is two adjacent hydrogen atoms, but R^2 may also be an alkyl group or

(b) may form another bond formed between the carbon atoms to which they are attached;

R^7 is a hydrogen atom, a hydroxy group, a protected hydroxy group, or an alkoxy group, or an oxo group together with R^1;

R^8 and R^9 are independently a hydrogen atom or a hydroxy group;

R^{10} is a hydrogen atom, an alkyl group, an alkyl group substituted by one or more hydroxy groups, an alkenyl group, an alkenyl group substituted by one or more hydroxy groups, or an alkyl group substituted by an oxo group;

X is an oxo group, (a hydrogen atom and a hydroxy group), (a hydrogen atom and a hydrogen atom), or a group represented by the formula $-CH_2O-$;

Y is an oxo group, (a hydrogen atom and a hydroxy group),

(a hydrogen atom and a hydrogen atom), or a group represented by the formula $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R^{11} and R^{12} are independently a hydrogen atom, an alkyl group, an aryl group or a tosyl group;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} are independently a hydrogen atom or an alkyl group;

R^{24} is an optionally substituted ring system which may contain one or more heteroatoms;

n is an integer of 1 or 2; and

in addition to the above definitions, Y, R^{10} and R^{23}, together with the carbon atoms to which they are attached, may represent a saturated or unsaturated 5- or 6-membered nitrogen, sulfur and/or oxygen containing heterocyclic ring optionally substituted by one or more groups selected from the group consisting of an alkyl, a hydroxy, an alkoxy, a benzyl, a group of the formula $-CH_2Se(C_6H_5)$, and an alkyl substituted by one or more hydroxy groups.

Preferable R^{24} may be cyclo(C_{5-7})alkyl group, and the following ones can be exemplified.

(a) a 3,4-di-oxo-cyclohexyl group;

(b) a $3-R^{20}-4-R^{21}$-cyclohexyl group,

in which R^{20} is hydroxy, an alkoxy group, an oxo group, or a $-OCH_2OCH_2CH_2OCH_3$ group, and

R^{21} is hydroxy, -OCN, an alkoxy group, a heteroaryloxy which may be substituted by suitable substituents, a $-OCH_2OCH_2CH_2OCH_3$ group, a protected hydroxy group, chloro, bromo, iodo, aminooxalyloxy, an azido group, p-tolyloxythiocarbonyloxy,

or $R^{25}R^{26}CHCOO-$,

in which R^{25} is optionally protected hydroxy or protected amino, and

R^{26} is hydrogen or methyl, or

R^{20} and R^{21} together form an oxygen atom in an epoxide ring; or

(c) cyclopentyl group substituted by methoxymethyl, optionally protected hydroxymethyl, acyloxymethyl (in which the acyl moiety optionally contains either a dimethylamino group which may be quaternized, or a carboxy group which may be esterified), one or more amino and/or hydroxy groups which may be protected, or aminooxalyloxymethyl. A preferred example is a 2-formyl-cyclopentyl group.

The definitions used in the above general formula (I) and the specific and preferred examples thereof are now explained and set forth in detail.

The term "lower" means, unless otherwise indicated, a group having 1 to 6 carbon atoms.

Preferable examples of the "alkyl groups" and an alkyl moiety of the "alkoxy group" include a straight or branched chain aliphatic hydrocarbon residue, for example, a lower alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, neopentyl and hexyl.

Preferable examples of the "alkenyl groups" include a straight or branched chain aliphatic hydrocarbon residue having one double-bond, for example, a lower alkenyl group such as vinyl, propenyl (e.g., allyl group), butenyl, methylpropenyl, pentenyl and hexenyl.

Preferable examples of the "aryl groups" include phenyl, tolyl, xylyl, cumenyl, mesityl and naphthyl.

Preferable protective groups in the "protected hydroxy groups" and the "protected amino" are 1-(lower alkylthio)-(lower)alkyl group such as a lower alkylthiomethyl group (e.g., methylthiomethyl, ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, butylthiomethyl, isobutylthiomethyl, hexylthiomethyl, etc.), more preferably C_1-C_4 alkylthiomethyl group, most preferably methylthiomethyl group;

trisubstituted silyl group such as a tri(lower)alkylsilyl (e.g., trimethylsilyl, triethylsilyl, tributylsilyl, tert-butyldimethylsilyl, tri-tert-butylsilyl, etc.) or lower alkyl-diarylsilyl (e.g., methyldiphenylsilyl, ethyldiphenylsilyl, propyldiphenylsilyl, tert-butyldiphenylsilyl, etc.), more preferably tri(C_1-C_4)alkylsilyl group and C_1-C_4 alkyldiphenylsilyl group, most preferably tert-butyldimethylsilyl group and tert-butyldiphenylsilyl group; and an acyl group such as an aliphatic, aromatic acyl group or an aliphatic acyl group substituted by an aromatic group, which are derived from a carboxylic acid, sulfonic acid or carbamic acid.

Examples of the aliphatic acyl groups include a lower alkanoyl group optionally having one or more suitable substituents such as carboxy, e.g., formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, carboxyacetyl, carboxypropionyl, carboxybutyryl, carboxyhexanoyl, etc.;

a cyclo(lower)alkoxy(lower)alkanoyl group optionally having one or more suitable substituents such as lower alkyl, e.g., cyclopropyloxyacetyl, cyclobutyloxypropionyl,

cycloheptyloxybutyryl, menthyloxyacetyl, menthyloxypropionyl, menthyloxybutyryl, menthyloxypentanoyl, menthyloxyhexanoyl, etc.; a camphorsulfonyl group; or a lower alkylcarbamoyl group having one or more suitable substituents such as carboxy or protected carboxy, for example, carboxy(lower)alkylcarbamoyl group (e.g., carboxymethylcarbamoyl, carboxyethylcarbamoyl, carboxypropylcarbamoyl, carboxybutylcarbamoyl, carboxypentylcarbamoyl, carboxyhexylcarbamoyl, etc.), tri-(lower)alkylsilyl(lower)alkoxycarbonyl(lower)alkylcarbamoyl group (e.g., trimethylsilylmethoxycarbonylethylcarbamoyl, trimethylsilylethoxycarbonylpropylcarbamoyl, triethylsilylethoxycarbonylpropylcarbamoyl, tert-butyldimethylsilylethoxycarbonylpropylcarbamoyl, tri-methylsilylpropoxycarbonylbutylcarbamoyl, etc.) and so on.

Examples of the aromatic acyl groups include an aroyl group optionally having one or more suitable substituents such as nitro, e.g., benzoyl, toluoyl, xyloyl, naphthoyl, nitrobenzoyl, dinitrobenzoyl, nitronaphthoyl, etc.; and
an arenesulfonyl group optionally having one or more suitable substituents such as halogen, e.g., benzenesulfonyl, toluenesulfonyl, xylenesulfonyl, naphthalenesulfonyl, fluorobenzenesulfonyl, chlorobenzenesulfonyl, bromobenzenesulfonyl, iodobenzenesulfonyl, etc.

Examples of the aliphatic acyl groups substituted by an aromatic group include ar(lower)alkanoyl group optionally having one or more suitable substituents such as lower alkoxy or trihalo(lower)alkyl, e.g., phenylacetyl, phenylpropionyl, phenylbutyryl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl, 2-ethyl-2-trifluoromethyl-2-phenylacetyl, 2-trifluoromethyl-2-propoxy-2-phenylacetyl, etc.

More preferable acyl groups among the aforesaid acyl groups are C_1-C_4 alkanoyl group optionally having carboxy, cyclo(C_5-C_6)alkoxy(C_1-C_4)alkanoyl group having two (C_1-C_4) alkyls at the cycloalkyl moiety, camphorsulfonyl group, carboxy-(C_1-C_4)alkylcarbamoyl group, tri(C_1-C_4)alkylsilyl(C_1-C_4)alkoxycarbonyl(C_1-C_4)-alkylcarbamoyl group, benzoyl group optionally having one or two nitro groups, benzenesulfonyl group having halogen, or phenyl(C_1-C_4)alkanoyl group having C_1-C_4 alkoxy and trihalo(C_1-C_4)alkyl group. Among these, the most preferable ones are acetyl, carboxypropionyl, menthyloxyacetyl, camphorsulfonyl, benzoyl, nitrobenzoyl, dinitrobenzoyl, iodobenzenesulfonyl and 2-trifluoromethyl-2-methoxy-2-phenylacetyl.

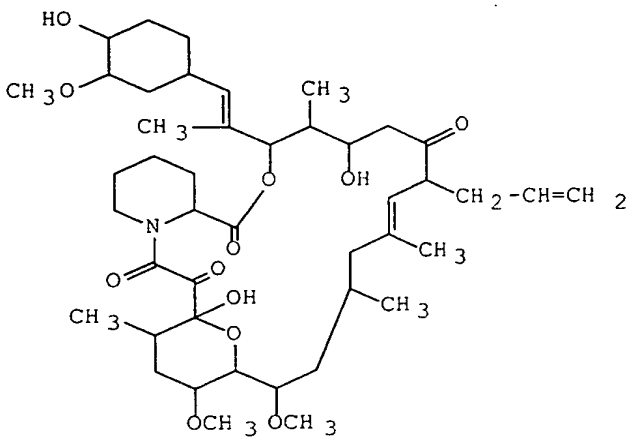
Preferable examples of the "5- or 6-membered nitrogen, sulfur and/or oxygen containing heterocyclic ring" include a pyrrolyl group and a tetrahydrofuryl group.

"A heteroaryl which may be substituted by suitable substituents" moiety of the "heteroaryloxy which may be substituted by suitable substituents" may be the ones exemplified for R^1 of the compound of the formula of EP-A-532,088, with preference given to 1-hydroxyethylindol -5-yl, the disclosure of which is incorporated herein by reference.

The ticyclic compounds (I) and its pharmaceutically acceptable salt for use in accordance with this invention are well known to have excellent immunosuppressive activity, antimicrobial activity and other pharmacological activities and, as such, be of value for the treatment or prevention of rejection reactions by transplantation of organs or tissues, graft-vs-

host diseases, autoimmune diseases, and infectious diseases [EP-A-0184162, EP-A-0323042, EP-A-423714, EP-A-427680, EP-A-465426, EP-A-480623, EP-A-532088, EP-A-532089, EP-A-569337, EP-A-626385, WO89/05303, WO93/05058, WO96/31514, WO91/13889, WO91/19495, WO93/5059, etc.], the disclosures of which are incorporated herein by reference.

Particularly, the compounds which are designated as FR900506 (=FK506), FR900520 (ascomycin), FR900523, and FR900525 are products produced by microorganisms of the genus Streptomyces, such as Streptomyces tsukubaensis No. 9993 [deposited with National Institute of Bioscience and Human Technology Agency of Industrial Science and Technology (formerly Fermentation Research Institute Agency of Industrial Science and Technology), at 1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki, Japan, date of deposit October 5, 1984, accession number FERM BP-927] or Streptomyces hygroscopicus subsp. yakushimaensis No. 7238 [deposited with National Institute of Bioscience and Human Technology Agency of Industrial Science and Technology (formerly Fermentation Research Institute Agency of Industrial Science and Technology), at 1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki, Japan, date of deposit January 12, 1985, accession number FERM BP-928][EP-A-0184162]. The FK506 (general name: tacrolimus) of the following chemical formula, in particular, is a representative compound.



Chemical name: 17-allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

The preferred examples of the tricyclic compounds (I) are the ones, wherein each of adjacent pairs of R^3 and R^4 or R^5 and R^6 independently form another bond formed between the carbon atoms to which they are attached;

each of R^8 and R^{23} is independently a hydrogen atom;

R^9 is a hydroxy group;

R^{10} is a methyl group, an ethyl group, a propyl group or an allyl group;

X is (a hydrogen atom and a hydrogen atom) or an oxo group;

Y is an oxo group;

each of R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{22} is a methyl group;

R^{24} is a 3-R^{20}-4-R^{21}-cyclohexyl group,

in which R^{20} is hydroxy, an alkoxy group, an oxo group, or a $-OCH_2OCH_2CH_2OCH_3$ group, and

R^{21} is hydroxy, -OCN, an alkoxy group, a

heteroaryloxy which may be substituted by suitable substituents, a $-OCH_2OCH_2CH_2OCH_3$ group, a protected hydroxy group, chloro, bromo, iodo, aminooxalyloxy, an azido group, p-tolyloxythiocarbonyloxy, or $R^{25}R^{26}CHCOO-$, in which R^{25} is optionally protected hydroxy or protected amino, and

R^{26} is hydrogen or methyl, or

R^{20} and R^{21} together form an oxygen atom in an epoxide ring; and

n is an integer of 1 or 2.

The most preferable tricyclic compounds (I) is, in addition to FK506, ascomycin derivatives such as halogenated-ascomycin (e.g., 33-epi-chloro-33-desoxyascomycin), which is disclosed in EP 427,680, example 66a.

The tricyclic compounds (I) has a similar basic structure, i.e., tricyclic macrolide structure, and at least one of the similar biological properties (for example, immunosupressive activity).

The tricyclic compounds (I) may be in a form of its salt, which includes conventional non-toxic and pharmaceutically acceptable salt such as the salt with inorganic or organic bases, specifically, an alkali metal salt such as sodium salt and potassium salt, an alkali earth metal salt such as calcium salt and magnesium salt, an ammonium salt and an amine salt such as triethylamine salt and N-benzyl-N-methylamine salt.

With respect to the macrolide compound used in the present invention, it is to be understood that there may be conformers and one or more stereoisomers such as optical and geometrical isomers due to asymmetric carbon atom(s) or double bond(s), and such conformers and isomers are also included within the scope of macrolide compound in the present invention. And further, the macrolide compounds can be in the form of a solvate or pro-drug, which is included within the scope of the present invention. The solvate preferably include a hydrate and an ethanolate.

The macrolide compounds usable in the present invention may be administered as pure compounds or mixtures of compounds or preferably, in a pharmaceutical vehicle or carrier.

The pharmaceutical compositions of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the tricyclic compounds of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external(topical), enteral, intravenous, intramuscular, or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable, carriers for tablets, pellets, capsules, eye drops, suppositories, solutions (saline, for example), emulsion, suspensions (olive oil, for example), ointment, aerosol sprays, cream, skin plasters, patches and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary,

stabilizing, thickening and coloring agents and perfumes may be used. The active object compound is included in the pharmaceutical composition in an effective amount sufficient to produce the desired effect upon the process or condition of the disease.

Mammals which may be treated using the method of the present invention include livestock mammals such as cows, horses, etc., domestic animals such as dogs, cats, rats, etc. and humans.

For applying this composition to a human, it is preferable to apply it by topical, especially by external, administration, particularly in the form of ointment, gel, lotion, aerosol sprays, cream, skin plasters or patches.

While the dosage of therapeutically effective amount of the macrolide compounds varies from and also depends upon the age and condition of each individual patient to be treated, a daily dose of about 0.0001-1000 mg, preferably 0.001-500 mg and more preferably 0.01-100 mg. of the active ingredient is generally given for treating diseases, and an average single dose of about 0.001-0.01mg, 0.2-0.5 mg, 1 mg, 5 mg, 10 mg, 50 mg, 100 mg, 250 mg and 500 mg is generally administered. Daily doses for chronic administration in humans will be in the range of about 0.1-0.3 mg/kg/day.

Especially, when applying externally, the recommended proportion of macrolide compound in the pharmaceutical composition is 0.001～20% (w/w), preferably 0.01～10%(w/w), of the total composition. And further, the macrolide compounds can be applied, simultaneously, separately or sequentially, with other agents having analgesic activity or immunosuppressive activity; such as, malononitrilamides(HMR 1279, HMR1715, etc), mycophenolate mofetil (CellCept), steroids, Azathiopurine, and

so on.

The following examples illustrate the present invention in further detail. It should be understood that those examples are not intended to limit the scope of the invention.

Example 1

FK506 Substance	0.1 g
propylene carbonate	5.00 g
liquid paraffin	11.0 g
solid paraffin	3.0 g
white bees wax	3.5 g
white petrolatum	q.s. (to 100.0 g)

The ointment composed of the above ingredients was prepared in a similar manner to that of the Example 1 described in EP-A-0474126.

Example 2

FK 506 Substance	1 g
Hydroxypropyl methylcellulose 2910 (TC-5R)	1 g
Lactose	2 g
Croscarmellose sodium (Ac-Di-Sol)	1 g

The FK 506 Substance (1 g) was dissolved in ethanol (10 ml), and thereto was added hydroxypropyl methylcellulose 2910 (TC-5R) (1 g) to prepare a suspension. To this suspension was added dichloromethane (5 ml) to prepare a homogeneous solution. Lactose (2 g) and croscarmellose sodium (Trade Mark: Ac-Di-Sol, maker: Asahi Chemical Industry) were homogeneously suspended to this solution, and then the organic solvent was removed by evaporation. The residual product was dried under reduced pressure for 10 hours by vacuum dryer, milled for 2

minutes by coffee mill and then passed through a sieve (32 mesh) to give the solid dispersion composition of FK 506 Substance (5 g). This composition was capsulated by a conventional manner to provide capsules containing 1 mg or 5 mg of FK 506 Substance per each capsule. This composition can be prepared in a similar manner to that of EP-A-0240773.

Example 3

Experiment

Young adult male Lister Hooded rats (Charles Rivers, UK) were maintained under standard animal house conditions, maximum 3 animals per cage, with access to food and water *ad lib*.

Unilateral arthritis was induced using the method described by Donaldson et al, J. Neurosci. Methods 31; 681-691 (1993). Briefly, the rat was anaesthetized with halothane (5% in oxygen) and 0.15 ml of Freund's complete adjuvant (Sigma; 1mg/ml heat killed mycobacterium tuberculosis) injected sub-dermally around the left ankle (tibio-tarsal) joint.

Measurement of pressure evoking reflex withdrawal of the limb when the joint was squeezed was undertaken using an pressure transducer (designed in-house) linked to a chart recorder and the mean of three consecutive pressure measurements made on each ankle, the right (control) joint being measured first. A tape measure was used for determining ankle circumference, and an infrared thermometer held against the joint used to provide a measure of temperature. Rats were weighed to provide an indication of general health.

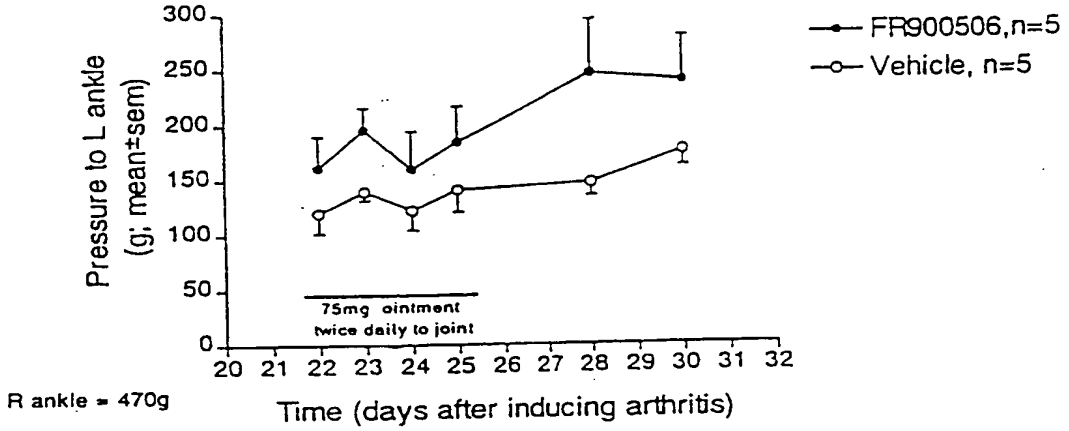
Drug treatment involved rubbing 75mg (pre-weighed) of ointment A, which is the same one prepared by the above-identified Example 1, or B (vehicle) into the left ankle joint

twice daily (at 09:00, 14:00) for five days. For the acute study, treatment started 24hrs before arthritis was induced (5 rats received FR900506, 5 received vehicle). For the chronic study, treatment started 21 days post-adjuvant, again with 5 rats per group. Measurements were made approximately 10 minutes after the afternoon application of ointment and took 30 minutes to complete.

Results

The analgesic effect of FR900506 is shown in Fig. 1. FR900506 has analgesic properties when applied topically to chronically hyperalgesic arthritic joints in the rat.

Fig. 1 Influence of FR900506 on joint hyperalgesia



The macrolide compound or its pharmaceutically acceptable salt was proved to have the analgesic effect, especially the topical analgesic effect, and thereby when administered systemically or topically is useful for treating and/or

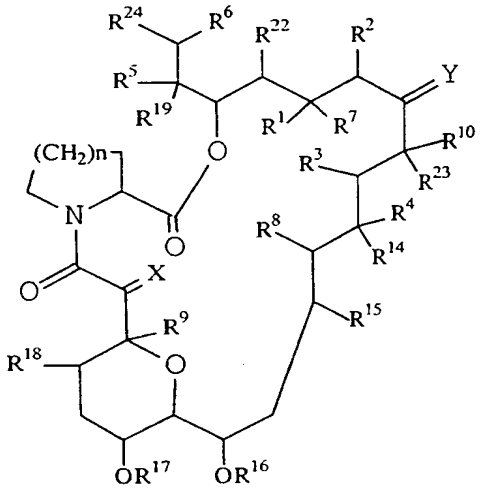
preventing pain(e.g., pain caused by arthritis(rheumatoid arthritis, acute rheumatic arthritis, gouty arthritis, psoriatic arthritis, etc)); arthralgia (intermittent arthralgia, periodic arthralgia, etc); hyperalgesia; allodynia (senile pruritus, etc); cutaneous manifestation of algesthesia caused by various diseases; and so on.

The patents, patent applications and publications cited herein are incorporated by reference.

CLAIMS

1. A use of macrolide compounds for manufacturing an agent for preventing or treating pain.

2. The use of Claim 1, in which the macrolide compounds is the tricyclic compounds of the following formula (I):



(I)

(wherein each of adjacent pairs of R^1 and R^2, R^3 and R^4 , and R^5 and R^6 independently

(a) is two adjacent hydrogen atoms, but R^2 may also be an alkyl group or

(b) may form another bond formed between the carbon atoms to which they are attached;

R^7 is a hydrogen atom, a hydroxy group, a protected hydroxy group, or an alkoxy group, or an oxo group together with R^1;

R^8 and R^9 are independently a hydrogen atom or a hydroxy group;

R^{10} is a hydrogen atom, an alkyl group, an alkyl group substituted by one or more hydroxy groups, an alkenyl group, an alkenyl group substituted by one or more hydroxy groups, or an alkyl group substituted by an oxo group;

X is an oxo group, (a hydrogen atom and a hydroxy group), (a

hydrogen atom and a hydrogen atom), or a group represented by the formula $-CH_2O-$;

Y is an oxo group, (a hydrogen atom and a hydroxy group), (a hydrogen atom and a hydrogen atom), or a group represented by the formula $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R^{11} and R^{12} are independently a hydrogen atom, an alkyl group, an aryl group or a tosyl group;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} are independently a hydrogen atom or an alkyl group;

R^{24} is an optionally substituted ring system which may contain one or more heteroatoms;

n is an integer of 1 or 2; and

in addition to the above definitions, Y, R^{10} and R^{23}, together with the carbon atoms to which they are attached, may represent a saturated or unsaturated 5- or 6-membered nitrogen, sulfur and/or oxygen containing heterocyclic ring optionally substituted by one or more groups selected from the group consisting of an alkyl, a hydroxy, an alkoxy, a benzyl, a group of the formula $-CH_2Se(C_6H_5)$, and an alkyl substituted by one or more hydroxy groups; or its pharmaceutically acceptable salt.

3. A method for preventing or treating pain, which comprises administering macrolide compounds to mammals.

4. A pharmaceutical composition for preventing or treating pain, which comprises macrolide compounds in admixture with a carrier or excipient.

5. A use of the macrolide compounds for preventing or treating pain.

6. The macrolide compound used in Claims 1 to 5 is FK 506 Substance or its hydrate.

7. A use of macrolide compounds for manufacturing an

analgesic for topical use.

8. A use of macrolide compounds for manufacturing a medicament for preventing or treating pain caused by arthritis.

9. The use of Claim 8, in which the medicament is for topical administration.